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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/722,096	11/22/2000	Ernest G. Hope	12531-002001	4236

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EXAMINER
YAEN, CHRISTOPHER H

ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/722,096	HOPE, ERNEST G.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *34-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I in Paper No. 9 is acknowledged.

2. The amendment filed 10/3/02 (paper no 9) is acknowledged and entered into the record.

3. Currently, claims 1-59 are pending, claims 34-58 are withdrawn from consideration as being drawn to a non-elected invention. Therefore, claims 1-33, and 59 are examined on the record.

4. This application contains claims 34-58 drawn to an invention non-elected in Paper No. 9. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. Claims 1-33, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. With regard to claims 1-33, and 59 reciting the term "composition", it is not clear as to the additional components of this "composition", because a composition implies two or more components. As currently interpreted, the composition only contains one item, namely, ex vivo cells. It is also noted that since the ex vivo expanded cells are not particularly pointed out and distinctly claimed, the term "composition" could also be interpreted as a mixture of different cell types. As such, the claim is rendered indefinite and unclear.

7. With regard to claim 1 reciting the term "selectively", it is unclear as to the degree of selection required. This is a relative term and as such the metes and bounds of the term cannot be adequately determined.

8. With regard to claims 12-13 reciting the term "antigen", there are many distinct antigens present on the surface of tumor vasculature, of which the claims have not particularly pointed out. It is unclear as to which antigen is intended and included with the scope of the claims. As such the metes and bounds of the term cannot be determined.

9. With regard to claim 18 reciting the phrase "or a part thereof", it is unclear as to which part is being referred. Because IL-12 receptor has many potential parts of fragments, it is unclear as to which "part" is encompassed by the claim. As such the metes and bounds of the phrase cannot be determined.

10. With regard to claim 32 reciting the term "immuno-modulator", it is unclear as to which modulator is encompassed by the term. For example, an antigen is considered an immune system modulator because it elicits an immune response. As such, the claim is rendered indefinite because the are numerous types of immuno-modulators that can be encompassed by the claim, of which the claim has not specifically pointed out.

Claim Rejections - 35 USC § 112, 1st paragraph

11. Claims 1-33, and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising cytokine induced killer cells (CIK), does not reasonably provide enablement for a composition comprising T cells or NK cells (in general), wherein the cells also comprise a regulable suicide

gene, and further comprising chemotherapeutic agents, agents (which include antibodies, bi-specific antibodies), compounds (which include covalently or non-covalently associated compounds such as toxins, antibodies, detectable labels, immuno-modulators, and radioactive compound), or immunomodulators. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or

lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The nature of the invention: The claimed invention is drawn to a composition comprising ex vivo expanded cells, wherein the cells comprise a regulable suicide gene which further comprises chemotherapeutics, agents, compounds or immunomodulators, wherein the ex-vivo expanded cells are derived from T-cells, NK cells, and are CIK cells.

The amount of direction or guidance present and the presence or absence of working examples: The working examples of the instant specification is drawn to the generation/isolation/expansion of CIK cells, the functional examination of the CIK cells (through the use of antibodies directed at various cell surface markers to MHC class I, T cells, and NK cells), the interruption of FasL localization to the surface, adaptive immunotherapy of CIK, the effects of rHSP47-GST on the protection from CIK mediated lysis, and the identification of a peptide present in both HLA-A and Hsp47, that is capable of protecting from CIK lysis. However, no where in the specification does it teach the identification of any particular antigen in which the CIK is able to associated or recognize, the specific recognition of specific HSPs other than HSP47, a receptor that is capable of recognizing IL-12, the combination of the ex-vivo expanded cells with chemotherapeutics compounds, agents in general, compounds, or immuno-modulators, or a cell that harbors a regulable suicide gene. Because there is a lack of such

disclosure, one of skill in the art would be forced into undue experimentation to make the invention commensurate in scope to the claims.

For example, the identification of the antigen to which CIKs are able to associate with is not such a simple task. It involves the purification of proteins that associate with CIKs and the screening of potential antigens located on the surface of tumor vasculature, of which there are numerous possibilities (see Denekamp J (Eur. J. Surg. Suppl 1991;561:21-26) and (Int. J. Radiat. Biol. 1991;60(1/2):401-408)) Further, HSPs are ubiquitous proteins of which there are many functionally and structurally distinct kinds. Further still, the specification has not taught to one of skill in the art how the combination of chemotherapeutics, agents in general, compounds, or immuno-modulators with ex-vivo expanded cells would have on the survival of and the functionality of the ex-vivo cells (i.e. stability of the cells, whether the cells are still capable of functioning in the presence of the different additional compounds, and what dosages, if the cells are able to tolerate, would be needed before toxicity to the cells would occure). And lastly, although it is well known in the art that the manufacture of a cell harboring a regulable suicide gene is possible, the gene which is involved must be known. The specification has made no indication as to which gene is intended to be encompassed by the claim. There are many typed of genes that can accomplish the desired goal, namely the self destruction of the ex vivo expanded cell, but the mechanism, the gene and the effects in the presence of other compounds and or agents many trigger the cell to self destruct before the composition of ex vivo expanded cells can affect its purpose.

The breadth of the claims and the quantity of experimentation needed: Given the lack of teaching in the way of working examples, the broad range of potential antigens encompassed by the claims, and the lack of disclosure concerning the chemotherapeutics, agents, compounds and immuno-modulators, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, and 9-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Lu PH *et al* (J. Immunol 1994 Aug; 153(4):1687-96, **IDS** AI). Claims are drawn to a composition comprising ex vivo expanded cell, wherein the cells are T, NK or CIK cells, wherein the cells recognize an antigen present on the tumor vasculature and during neoangiogenesis, wherein the antigen recognition is non-MHC restricted/MHC independent, wherein the cells express a cell-surface receptor that recognizes HSP47, HLA, IL-12, or HSPs. The claims are also drawn to a composition that comprise ex vivo expanded cells that comprise cells that express CD3 and CD56, and cells that are capable of killing tumor cells. It is noted that the intended usage of the composition does not bear any patentable weight, and therefore the claims are simple drawn to a composition of ex vivo expanded cells, with the limitations set forth above.

Lu PH *et al* teach ex vivo expanded cell that are T cell and NK cell derived, wherein the cells express CD3 and CD56 leading to the generation of CIK cells. Lu PH *et al* also teach that these CIK cells are independent of MHC class I type response and therefore a non-MHC class I response. Lu PH *et al* further teach that these CIK cells are capable of killing tumor cells. Although Lu PH *et al* do not specifically teach the recognition of specific antigens, nor do they teach the expression of specific receptors, the fact that the cells are derived from a natural source and that because in the absence of evidence to the contrary, the cells inherently are able to recognize antigens present on the surface of tumor vasculature and neoangiogenic vessels. Furthermore, the cells also inherently contain receptors that recognize HSP47, HLA, IL-12, or HSPs.

Conclusion

14. No claim is allowed.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Alvarnes J.C. *et al* (Blood 1996 ;88(10) suppl. 1 Part 1-2: 39B, abstract #2882) teach the function of CIK in the lysis of HUVEC and tumor cell targets and concludes by saying that CIK mediated lysis is mediated through perforin and grazyme induced cytolysis.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
December 13, 2002